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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/043,440	01/10/2002	Costas D. Maranas	P05468US1	1336

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EXAMINER

MORAN, MARJORIE A

ART UNIT	PAPER NUMBER
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1631

DATE MAILED: 06/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/043,440

Applicant(s)

MARANAS ET AL.

Examiner

Marjorie A. Moran

Art Unit

1631

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 April 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-19 is/are pending in the application.
- 4a) Of the above claim(s) 9, 17 and 18 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-8, 10-16 and 19 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 1/10, 3/22, 11/25/02.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

Election/Restrictions

Applicant's election of Group I, claims 1-16 and 19, and Specie (A), directed to logic constraints defined by a relationship between changes in reaction fluxes and metabolic concentrations in the reply filed on 4/1/04 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 9 and 17-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species or Invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 4/1/04.

An action on the merits of elected claims 1- 8, 10-16 and 19, as they read on the elected specie, follows.

Information Disclosure Statement

The IDS's filed 1/10/02, 3/22/02 and 11/25/02 have been considered in full. Where references were cited multiple times, one citation was initialed to indicate consideration and all other citations of the same reference were crossed out.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 limits constraints listed in claim 1 to be connectivity constraints. However, parent claim 1 limits constraints to a recited list which does not include connectivity constraints. It is unclear whether applicant intends the list of constraints of claim 1 to further comprise connectivity constraints, intends to further limit all of the constraints of claim 1 to be connectivity constraints, or intends some sort of subset of constraints, therefore the claim is indefinite. For purposes of search and examination, a "connectivity constraint" is interpreted to be one of those recited in claim 1.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 3-6, 8, 12-16 and 19 are rejected under 35 U.S.C. 102(a) as being anticipated by EDWARDS et al. (IDS ref: BMC Bioinformatics (2000) vol. 1:1, pages 1-10).

EDWARDS teaches a method and system for modeling E. coli metabolism by constructing a flux balance analysis model and applying constraints to the model, and teaches that the model may be defined by cellular constraints (or barriers); specifically

include kinetic or gene regulatory constraints (pp. 2-3), thus anticipating claims 1, 3, 6, and 19. EDWARDS teaches use of mixed-integer linear programming to calculate a desired metabolic outcome, specifically to calculate a minimal set of metabolic reactions to achieve particular growth rates (p. 3), thus anticipating claims 4-5 and 12-15. EDWARDS teaches in silico examples of genetic engineering and calculation of a relationship between metabolic concentrations of cofactors and changes in reaction fluxes (pp. 4-5 and tables), thus anticipating claims 8 and 16.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8, 10-16 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over EDWARDS et al. (IDS ref: BMC Bioinformatics (2000) vol. 1:1, pages 1-10) in view of SCHILLING et al. (IDS ref: PNAS (4/1998) vol. 95, pp. 4193-4198).

Claims 1, 6, and 19 recite methods and a system for modeling cellular metabolism of an organism by constructing a flux balance analysis model and applying constraints to the model. Claims 1, 3, and 19 further limit the constraints to those of a recited list. Claims 2 and 6-7 further limit the constraints to be logic constraints, specifically those which protect against violation of a kinetic or regulatory barrier. Claims 4-5 and 14-15 further limit the methods to applying mixed-integer linear programming to solve for a desired metabolic outcome and solving for a desired metabolic outcome. Claims 12 and 13 limit the method of claim 6 to further comprise a computational procedure to identify a minimal set of metabolic reactions and to identify a minimal set of reactions to support a selected growth rate. Claim 8 limits the method of claim 6 to one wherein logic constraints are defined by a relationship between changes in reaction fluxes and metabolic concentrations. Claim 10 limits the logic constraints to be represented by binary variables.

EDWARDS teaches a method and system for modeling E. coli metabolism by constructing a flux balance analysis model and applying constraints to the model, as set forth above. EDWARDS teaches that his "feasible set" of reactions is subject to cellular constraints (p. 3), does not specifically teach selecting constraints to protect against a violation of a kinetic or regulatory barrier. EDWARDS does not teach binary variables.

SCHILLING teaches flux balance analysis of metabolic reactions in cells using linear programming wherein only vectors (pathways) which are biochemically feasible are included (p. 4195). SCHILLING also teaches that his programming includes binary variables (p. 4195). SCHILLING teaches that all reactions have a value of 1 (p. 4195), therefore a value of 0 necessarily represents the absence of a reaction.

It would have been obvious to one of ordinary skill in the art at the time of invention to have protected against barrier violating (or biochemically impossible) pathways in the method of EDWARDS by using constraints which allow for only biochemically feasible pathways, as taught by SCHILLING, where the motivation would have been to constrain flux analysis to be both feasible and biochemically meaningful, as taught by SCHILLING (p. 4195). It would further have been obvious to have used the binary variables of SCHILLING in the linear programming computations of EDWARDS where the motivation would have been to facilitate vector transformation in the method, as taught by SCHILLING (p. 4195, right column).

Conclusion

Claims 1- 8, 10-16 and 19 are rejected; claims 9 and 17-18 are withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marjorie A. Moran whose telephone number is (571) 272-0720. The examiner can normally be reached on Mon. to Wed, 7:30-4; Thurs 7:30-6; Fri 7-1 EST.

Art Unit: 1631

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571)272-0722. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marjorie A. Moran
Primary Examiner
Art Unit 1631

Marjorie A. Moran
6/10/04

mam